Opioid-Associated Drug-Drug Interactions: What We Don't Know is Hurting Us

Andrew J. Saxon, MD
With acknowledgements to
Elinore F. McCance-Katz, MD, PhD
Dr. Saxon, Disclosures

- Received royalties as Section Editor, UpToDate
AAAP aims to provide educational information that is balanced, independent, objective and free of bias and based on evidence. In order to resolve any identified Conflicts of Interest, disclosure information from all planners, faculty and anyone in the position to control content is provided during the planning process to ensure resolution of any identified conflicts. This disclosure information is listed below:

The following developers and planning committee members have reported that they have no commercial relationships relevant to the content of this webinar to disclose: AAAP CME/CPD Committee Members Dean Krahn, MD, Kevin Sevarino, MD, PhD, Tim Fong, MD, Tom Kosten, MD, Joji Suzuki, MD and AAAP Staff Kathryn Cates-Wessel, Miriam Giles, Sharon Joubert Frezza, and Justina Andonian.

All faculty have been advised that any recommendations involving clinical medicine must be based on evidence that is accepted within the profession of medicine as adequate justification for their indications and contraindications in the care of patients. All scientific research referred to, reported, or used in the presentation must conform to the generally accepted standards of experimental design, data collection, and analysis. Speakers must inform the learners if their presentation will include discussion of unlabeled/investigational use of commercial products.
Target Audience

• The overarching goal of PCSS-O is to offer evidence-based trainings on the safe and effective prescribing of opioid medications in the treatment of pain and/or opioid addiction.

• Our focus is to reach providers and/or providers-in-training from diverse healthcare professions including physicians, nurses, dentists, physician assistants, pharmacists, and program administrators.
Educational Objectives

At the conclusion of this activity participants should be able to:

• Review of current epidemiologic data on drug-drug interactions between opioids and other medications

• Review possible explanations for increases in drug-drug interactions

• Review physiological and pharmacokinetic basis for adverse drug interactions

• Identify strategies for reducing risk
Adverse Drug Interactions

- Accidental deaths are the leading cause of death in those aged 1-44 with highest rates in 25-44 y.o.

- Poisoning is now leading cause of accidental deaths; 145% increase in poisoning deaths 1999-2007; opioids most frequently named drug in poisonings

Adverse Drug Interactions

• Adverse drug interactions involving opioids:
  - Overdose
  - Combining medications
    - E.g.: heroin or methadone or buprenorphine or opioid analgesics:
      - With other prescribed medications
      - With illicit substances
      - With alcohol
Distribution of first-listed specified drugs among unintentional drug overdose deaths, US, 2005

- Methadone, 16.2%
- Other opioid painkillers, 22.0%
- Benzodiazepine/antidepressants, 6.5%
- Cocaine, 25.1%
- Heroin, 7.7%
- Methamphetamine, 6.4%
- Other specified drugs, 16.1%
Drug Poisoning Death Rates 1999-2012

Figure 1. Age-adjusted drug-poisoning death rates: United States, 1999–2012

NOTE: Drug-poisoning deaths may involve both opioid analgesics and heroin.
Drugs Mentioned with Methadone

Methadone only (38%)
alcohol
alprazolam
carisoprodol
clonazepam
cocaine
Duloxetine, amitriptyline
Fluoxetine, trazodone
heroin
hydrocodone
marijuana
MDMA (ecstasy)
methamphetamine
morphine
narcotic analgesics
olanzapine
oxycodone
quetiapine
unspecified benzodiazepines
zolpidem

RADARS DEATHS (2003-2008)

Methadone only (33%)
alcohol (7%)
amitriptyline (8%)
atypical antipsychotics (9%)
Benzodiazepines (52%)
cocaine (7%)
hydrocodone (7%)
other anticonvulsant (7%)
other narcotic (8%)
SSRIs (8%)

Methadone-Associated Adverse Effects

From Maxwell and McCance-Katz, 2010
DAWN ED-2007
Buprenorphine+Naloxone
buprenorphine+naloxone only (40%)
alcohol
alprazolam
bupropion
carisoprodol
clonazepam
clonidine
cocaine
cyclobenzaprine
fentanyl
heroin
hydrocodone
hydromorphone
lithium
lorazepam
marijuana
methadone
modafinil
other benzodiazepines
oxycodone
paroxetine
quetiapine
risperidone
sertaline
trazadone
zolpidem

DAWN ED-2007
Buprenorphine Only
alcohol
alprazolam
citalopram
clonidine
cocaine
dextromethorphan+quaifenesin
heroin
hydrocodone
marijuana
methadone
morphine
olazapine
other benzodiazepines
other narcotics
oxycodone
quetiapine
tramadol
ziprasidone

Buprenorphine-Associated Adverse Effects

From Maxwell and McCance-Katz, 2010
Underlying Reasons for Drug-Drug Interactions

- Increasing numbers receive opioid analgesics for pain
- Many with pain have co-occurring medical and/or mental disorders
- Patients believe prescribed drugs are ‘safe’
- Lack of patient education about adverse events that can occur
- May not understand need to take as prescribed
- Sharing/selling
Pathophysiology of Drug-Drug Interactions

- Pharmacokinetic: what the body does to the drug (or not)
- Pharmacodynamic: what the drug or drugs do to the body
Pharmacokinetic Interactions

- Drug (in presence of other drugs)
  - May be better absorbed; e.g.: slowed GI motility
  - Altered efflux (Pgp effects)
  - Inhibition or induction of metabolism; CYP enzymes or glucuronidation effects
- Net increase in exposure to drug(s) or reduction to the point of inducing physical withdrawal
- E.g.: Ciprofloxacin inhibition of methadone metabolism
  Rifampin induction of buprenorphine metabolism

Rifampin effect on buprenorphine PK. McCance-Katz et al., 2011
Pharmacodynamic Interactions

- PK interactions may have associated pharmacodynamic consequences
- Pharmacodynamic interactions can occur in the absence of a PK interaction
- Two drugs with similar pharmacological characteristics interact synergistically
  - Increases potential toxicity of drug
- Opioids and benzodiazepines
  - E.g.: alprazolam with buprenorphine
- Opioids and alcohol
Opioids and Other Drugs: Basis of Adverse Events

• Why are we seeing adverse events and increasing deaths in methadone-using individuals who co-consume psychotropics: SSRIs, antipsychotics?

• Not formally studied, but…
  – Drug Abuse Warning Network (DAWN) and Medical Examiner (ME) data describe increasing numbers
  – Methadone metabolized by CYP 3A4, 2D6, 2B6, buprenorphine metabolized by mainly 3A4
  – Some SSRIs and some antipsychotics can inhibit metabolic enzymes
  – May lead to increased plasma concentrations of drugs and associated toxicities
  – E.g.: fluoxetine and fluvoxamine: inhibit both 3A4 and 2D6
  – paroxetine, sertraline, citalopram, and escitalopram: inhibit CYP 2D6 only
Opioids and Other Drugs: Basis of Adverse Events

- Methadone linked to blockade of hERG channels that has been reported to increase risk for arrhythmia (Torsade de Pointes)

- As methadone concentrations rise; risk of adverse events increases
  - High dose (> 100 mg/d methadone)
  - Drug interactions that increase methadone exposure through inhibition of methadone metabolism
    - (e.g.: fluvoxamine/methadone interaction)
  - Drug interactions that occur when an inducing drug is given; methadone dose increased to maintain efficacy; then the drug is withdrawn and methadone dose is not concomitantly lowered
    - E.g.: lopinavir/ritonavir/methadone interaction
Avoiding Adverse Interactions

• Think about metabolic interactions

• Warn patients/families about toxicities: cognitive impairment, increased sedation, slowed, loud breathing

• If concomitant medications are needed; try to use medications less likely to impair opioid metabolism
  - Methadone: venlafaxine, SSRIs excluding fluoxetine/fluvoxamine
  - Buprenorphine: mainly 3A4 substrate; avoid fluoxetine/fluvoxamine

• Buprenorphine may be preferable to methadone in those needing other medications because there are fewer expected interactions, but there are few data to confirm this supposition
# Potential Methadone Drug-Drug Interactions

<table>
<thead>
<tr>
<th>Class or Specific Drug</th>
<th>Interaction</th>
<th>Putative Mechanism</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Antiretrovirals:</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Efavirenz, Lopinavir, Nevirapine</td>
<td>Reduction in serum methadone levels</td>
<td>Induction of CYP 450 3A4</td>
<td>Clinically significant opioid withdrawal symptoms likely</td>
</tr>
<tr>
<td>Abacavir, Etravirine, Nelfinavir, Ritonavir, Squinavir, Tipranavir</td>
<td>May reduce serum methadone levels</td>
<td>Induction of CYP 450 3A4</td>
<td>Clinically pertinent opioid withdrawal symptoms usually not seen with these agents</td>
</tr>
<tr>
<td>Didanosine, Stavudine</td>
<td>Reduction in didanosine, stavudine plasma concentration</td>
<td>Decreased bioavailability</td>
<td>Possible decreased efficacy of didanosine, stavudine</td>
</tr>
<tr>
<td>Zidovudine</td>
<td>Increase in zidovudine plasma concentration</td>
<td>Unknown</td>
<td>Risk of zidovudine toxicity</td>
</tr>
<tr>
<td>Delavirdine</td>
<td>Increased methadone serum concentration</td>
<td>Inhibition of CYP 450 3A4</td>
<td>No clinically meaningful adverse events observed</td>
</tr>
</tbody>
</table>
# Potential Methadone Drug-Drug Interactions

<table>
<thead>
<tr>
<th>Class or Specific Drug</th>
<th>Interaction</th>
<th>Putative Mechanism</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Antidepressants</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Tricyclics:</strong> amitriptyline, clomipramine, desipramine, doxepin, imipramine, nortriptyline, protriptyline, trimipramine</td>
<td>Increases risk for constipation and sedation. Increases risk for QT prolongation and arrhythmia</td>
<td>Anticholinergic effects. Blockade of hERG channel.</td>
<td>Clinical experience with combination indicates it is generally safe with careful clinical monitoring.</td>
</tr>
<tr>
<td><strong>Serotonin reuptake inhibitors:</strong></td>
<td></td>
<td>Inhibition of CYP 450 3A4, 2D6. Blockade of serotonin transporter.</td>
<td>Clinical experience with combination indicates it is generally safe with careful clinical monitoring.</td>
</tr>
</tbody>
</table>
## Potential Methadone Drug-Drug Interactions

<table>
<thead>
<tr>
<th>Class or Specific Drug</th>
<th>Interaction</th>
<th>Putative Mechanism</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Antidepressants</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Monoamine oxidase inhibitors: Isocarboxazid, phenelzine, selegiline, tranylcypromine</td>
<td>Increased risk for serotonin syndrome.</td>
<td>Inhibition of serotonin metabolism.</td>
<td>Use with extreme caution and careful clinical monitoring.</td>
</tr>
<tr>
<td>Serotonin/norepinephrine reuptake inhibitors: Duloxetine, desvenlafaxine, venlafaxine</td>
<td>Increased risk for serotonin syndrome. Increases risk for QT prolongation and arrhythmia (venlafaxine)</td>
<td>Blockade of serotonin transporter. Blockade of hERG channel (venlafaxine).</td>
<td>Clinical experience with combination indicates it is generally safe with careful clinical monitoring.</td>
</tr>
</tbody>
</table>
# Potential Methadone Drug-Drug Interactions

<table>
<thead>
<tr>
<th>Class or Specific Drug</th>
<th>Interaction</th>
<th>Putative Mechanism</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Antibiotics:</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ciprofloxacin, clarithromycin,</td>
<td>May increase methadone serum levels. Increases risk for QT prolongation and</td>
<td>Inhibition of CYP 450 3A4. Blockade of hERG channel</td>
<td>One case report of sedation (ciprofloxacin). Clinical monitoring</td>
</tr>
<tr>
<td>erythromycin, azithromycin</td>
<td>arrhythmia</td>
<td></td>
<td>required.</td>
</tr>
<tr>
<td><strong>Rifampin</strong></td>
<td>Reduction serum methadone levels</td>
<td>Induction of CYP 450 3A4</td>
<td>Severe opioid withdrawal can occur. Will need increased methadone</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>dose. Or switch antibiotics (e.g. rifabutin)</td>
</tr>
<tr>
<td><strong>Antifungals:</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ketoconazole, fluconazole,</td>
<td>May increase methadone serum levels.</td>
<td>Inhibition of CYP 450 3A4</td>
<td>Little evidence for important clinical effects</td>
</tr>
<tr>
<td>voriconizole</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
### Potential Methadone Drug-Drug Interactions

<table>
<thead>
<tr>
<th>Class or Specific Drug</th>
<th>Interaction</th>
<th>Putative Mechanism</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Anticonvulsants:</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Carbamazepine, phenytoin</td>
<td>Reduction in serum methadone levels</td>
<td>Induction of CYP 450 3A4</td>
<td>Severe opioid withdrawal can occur. Will need increased methadone dose.</td>
</tr>
<tr>
<td><strong>Antiarrhythmics:</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Procainamide, quinidine</td>
<td>Increases risk for QT prolongation and arrhythmia</td>
<td>Blockade of hERG channel</td>
<td>Careful clinical monitoring required</td>
</tr>
<tr>
<td>Amiodarone</td>
<td>May increase methadone serum levels. Increases risk for QT prolongation and arrhythmia</td>
<td>Inhibition of CYP 450 3A4. Blockade of hERG channel</td>
<td>Careful clinical monitoring required</td>
</tr>
</tbody>
</table>
## Potential Methadone Drug-Drug Interactions

<table>
<thead>
<tr>
<th>Class or Specific Drug</th>
<th>Interaction</th>
<th>Putative Mechanism</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Benzodiazepines</td>
<td>Additive CNS and respiratory depressant effects</td>
<td>Increased GABA activity</td>
<td>Careful clinical monitoring required</td>
</tr>
<tr>
<td>Barbiturates</td>
<td>Additive CNS and respiratory depressant effects</td>
<td>Increased GABA activity</td>
<td>Careful clinical monitoring required</td>
</tr>
<tr>
<td>Quetiapine</td>
<td>May increase methadone serum levels</td>
<td>Inhibition of CYP 450 2D6</td>
<td>Careful clinical monitoring required</td>
</tr>
<tr>
<td>Cimetidine</td>
<td>May increase methadone serum levels.</td>
<td>Inhibition of CYP 450 3A4</td>
<td>No evidence major clinical effect</td>
</tr>
<tr>
<td>Naltrexone</td>
<td>Precipitated opioid withdrawal</td>
<td>Displaces methadone from µ-opioid receptors</td>
<td>Contraindicated</td>
</tr>
</tbody>
</table>
Potential Buprenorphine Drug-Drug Interactions

- The following interactions are notable (mechanisms similar to those for methadone):
  - Delavirdine, **Atazanavir**
    - Atazanavir does **not** appear to increase methadone levels
  - Rifampin
  - Benzodiazepines
Potential Buprenorphine Drug-Drug Interactions

• Buprenorphine not as susceptible as methadone to drug-drug interactions
  – Tighter binding to receptor may make blood levels less important
  – Has an active metabolite, nor-buprenorphine
  – Partial agonist effect may mitigate some pharmacodynamic interactions and reduce risk from elevated blood levels
  – Does not prolong QT interval on ECG

• Many potential buprenorphine interactions have not been studied
Strategies

• Training of prescribers:
  - Non-opioid strategies to effectively control pain
  - Safe prescribing
  - Avoid polypharmacy whenever possible

• Public outreach and education
  - E.g.: Important information about how medications interact including basic pharmacology of opioids
  - No medication sharing
  - How to safely dispose of medications—and this should be available at no charge to patients

• Use of Providers’ Clinical Support System for Medication Assisted Treatment (PCSS-MAT)
  - www.pcssmat.org

• Use of Providers’ Clinical Support System for Opioid Therapies (PCSS-O)
  - www.pcss-o.org
References


References

• Federation of State Medical Boards, 2004


References


- NIDA Research Report Series, 2004
PCSS-O Colleague Support Program and Listserv

- PCSS-O Colleague Support Program is designed to offer general information to health professionals seeking guidance in their clinical practice in prescribing opioid medications.
- PCSS-O Mentors comprise a national network of trained providers with expertise in addiction medicine/psychiatry and pain management.
- Our mentoring approach allows every mentor/mentee relationship to be unique and catered to the specific needs of both parties.
- The mentoring program is available at no cost to providers.

For more information on requesting or becoming a mentor visit: [http://pcss-o.org/colleague-support/](http://pcss-o.org/colleague-support/)

- Listserv: A resource that provides an “Expert of the Month” who will answer questions about educational content that has been presented through PCSS-O project. To join email: pcss-o@aaap.org.
PCSS-O is a collaborative effort led by American Academy of Addiction Psychiatry (AAAP) in partnership with: American Dental Association (ADA), American Medical Association (AMA), American Osteopathic Academy of Addiction Medicine (AOAAM), American Psychiatric Association (APA), American Society for Pain Management Nursing (ASPMN), and International Nurses Society on Addictions (IntNSA).

For more information visit: www.pcss-o.org
For questions email: pcss-o@aaap.org

Twitter: @PCSSProjects

Funding for this initiative was made possible (in part) by Providers’ Clinical Support System for Opioid Therapies (grant no. H79TI023439) from SAMHSA. The views expressed in written conference materials or publications and by speakers and moderators do not necessarily reflect the official policies of the Department of Health and Human Services; nor does mention of trade names, commercial practices, or organizations imply endorsement by the U.S. Government.